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Patent
Case No.: HA160a

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 4,217,347
Issue Date: August 12, 1980
For: Method of Treating Hypertension and Medicaments Thereof
Inventors: Zola P. Horovitz, Bernard Rubin
Assignee: E. R. Squibb & Sons, Inc.

Princeton, New Jersey 08540

December 6, 1984

APPLICATION FOR EXTENSION OF TERM OF

UNITED STATES PATENT 4,217,347

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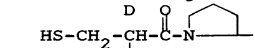
To the Commissioner of Patents and Trademarks:

In accordance with the provisions of 35 U.S.C. 156, E. R. Squibb & Sons, Inc., a corporation of the state of Delaware, having a place of business at Lawrenceville-Princeton Road, Lawrenceville, New Jersey 08540 (hereinafter referred to as "Squibb") hereby applies for an extension of 14 months of the term of United States patent 4,217,347, issued August 12, 1980.

The following items are relevant, and follow the guidelines set forth by the United States Patent and Trademarks Office at 1047 O.G. 16:

1) This application for extension is based upon the regulatory review period before the Food and Drug Administration of Squibb's Capozide® product. Capozide® is a combination of captopril and hydrochlorothiazide. The package insert for the product is attached hereto.

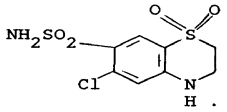
Captopril is designated chemically as 1-(D-3-mercapto-2-methyl-1-oxopropyl)-L-proline and has the following structure:



S2607 12/10/84 4217347 19-3880 1 111 750.00CH

RW10126 06/05/87 4217347 19-3880 010 111 200.00CR

Hydrochlorothiazide is designated as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide, 1,1-dioxide and has the following structure:



2) Regulatory review of Capozide® occurred under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355).

3) Capozide® received permission for commercial marketing and use under Section 505 of the Federal Food, Drug, and Cosmetic Act on October 12, 1984.

4) This application for extension of the term of United States patent 4,217,347 is being submitted within the 60 day period beginning on October 12, 1984. The last day on which the application could be submitted is December 11, 1984.

5) This application for extension of patent term seeks to extend the term of United States patent 4,217,347, issued August 12, 1980. This patent has <u>not</u> been previously extended. The inventors named in the patent are Zola P. Horovitz, of Princeton, New Jersey and Bernard Rubin, of Lawrenceville, New Jersey. The application is assigned to Squibb by an assignment recorded on February 11,

1980 in the United States Patent and Trademark Office at Reel 3731, Frame 223.

6) Attached hereto is a copy of United States patent 4,217,347 in the form specified in the guidelines of the United States Patent and Trademark Office set forth at 1047 O.G. 16.

7) Attached hereto is a copy of a Certificate of Correction issued in connection with United States patent 4,217,347 on February 3, 1981.

8) United States patent 4,217,347 claims Capozide® and a method for reducing blood pressure using Capozide®. Capozide® tablets come in four different strengths, labeled arbitrarily below as A, B, C and D. The package insert for Capozide® directs that a tablet be taken orally by the patient two (2) or three (3) times daily. The available dosages are:

	Captopril	Hydrochlorothiazide
A)	50mg.*	15mg.
B)	25mg.	15mg.
C)	50mg.	25mg.
D)	25mg.	25mg.

*mg. = milligrams

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 each includes within its scope a method for reducing blood pressure (the approved use for Capozide®) which comprises the oral administration (Capozide® has been approved as tablets for oral administration) to a mammalian species having elevated blood pressure (Capozide® has

been approved for use by humans with elevated blood pressure) of a combination comprising a compound having a specific structural formula (each of the above claims includes captopril within its scope) and a diuretic which is specified (each of the above claims includes hydrochlorothiazide within its scope). The narrowest of the above claims set forth a daily dosage of 30 to 300mg. of captopril (or other specified compound) and 15 to 200mg. of hydrochlorothiazide (or other specified diuretic). These claims encompass the daily dosage of each of the above-listed formulations as, of course, do the claims having broader dosage ranges.

Claims 12, 13, 14, 15, 16, 17, 18, 19 and 20 each includes within its scope an oral antihypertensive composition (Capozide® has been approved as tablets for oral administration for the treatment of elevated blood pressure, which is also known as hypertension) comprising a combination of a compound having a specific structural formula (each of the above claims includes captopril within its scope) and a diuretic which is specified (each of the above claims includes hydrochlorothiazide within its scope) and a physiologically acceptable carrier (Capozide® utilizes physiologically acceptable carriers). Claims 12, 14, 15, 16, 17, 18 and 19 specify that the composition comprises 15 to 600mg. of captopril (or related compound) and 15

to 300mg. of hydrochlorothiazide (or other specified diuretic). Claims 13 and 20 have a narrower dosage range. Each of claims 12 to 20 encompass the tablets of formulations "A" and "C" as set forth above.

Claims 22 and 25 each includes within its scope an oral antihypertensive composition (Capozide® has been approved as tablets for oral administration for the treatment of elevated blood pressure, which is also known as hypertension) comprising a combination of a compound having a specific structural formula (each of the above claims includes captopril within its scope) and a diuretic which is specified (each of the above claims includes hydrochlorothiazide within its scope) and a physiologically acceptable carrier (Capozide® utilizes physiologically acceptable carriers). Both claims specify that the composition comprises about 5 to 125mg. of captopril (or related compound) and 2.5 to 50mg. of hydrochlorothiazide (or other specified diuretic). This encompasses the tablets of all formulations as set forth above.

9) The relevant dates and information pursuant to 35 U.S.C. 156(g) that will enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

For 35 U.S.C. 156(g)(1)(B)(i) -

The Investigational New Drug Application (number 17-652) for Capozide®, an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Acid, was filed June 13, 1980, and became effective July 13, 1980.

The New Drug Application (number 18-709) for Capozide®, under section 505 of the Federal Food, Drug, and Cosmetic Act, was filed April 23, 1982.

For 35 U.S.C. 156(g)(1)(B)(ii) -

The New Drug Application (number 18-709) for Capozide®, under section 505 of the Federal Food, Drug, and Cosmetic Act, was filed April 23, 1982.

The New Drug Application (number 18-709) for Capozide®, under Section 505 of the Federal Food, Drug, and Cosmetic Act, was approved October 12, 1984.

10) The following is a brief description of the activities undertaken by Squibb during the applicable regulatory review period with respect to Capozide® including the dates applicable to such activities.

June 13, 1980	Investigational New Drug Application 17,652 was filed. This provided for studies under protocol 17,652-1.
July 14, 1980	First clinical supplies were shipped.

July 15, 1980	Modifications to protocol 17,652-1 were submitted.
August 15, 1980	First patient was treated.
November 7, 1980	Protocol-1 was revised and redesignated as 17,652-1A. In addition, Protocol 17,652-3 was submitted.
December 5, 1980	Report on additional animal studies was submitted.
March 12, 1981	An addendum to protocol 17,652-1A was submitted providing for long-term therapy.
April 13, 1981	Protocols 17,652-4 and 17,652-5 were submitted.
June 17, 1981	Information concerning methods for assaying captopril in blood and urine samples were submitted.
September 9, 1981	Protocol 17,652-6 was submitted.
January 20, 1982	A modification of protocol 17,652-6 was submitted.
February 4, 1982	Highlights of the clinical studies carried out on this combination were submitted in a progress report.
February 9, 1982	Protocol 17,652-7 was submitted.
April 23, 1982	New Drug Application 18-709 was filed.
November 30, 1982	Additional manufacturing and control details, requested verbally on September 30, 1982, were submitted.
June 1, 1983	Additional manufacturing and control details, requested verbally on May 6, 1983, were submitted.
September 30, 1983	Additional manufacturing and control details, verbally requested at a meeting between Squibb and FDA representatives on

	September 28, 1983, were submitted.
October 17, 1983	A modified commitment for stability studies on market lots of the product, verbally requested on October 13, 1983, was submitted.
December 28, 1983	Submitted supplement to NDA 18-343 (captopril tablets) including report of protocl 12,918-130, providing for treatment of hypertension using a twice-daily regimen.
February 9, 1984	Additional statistical information from protocols 17,652-6 and 12,928-130 was submitted to NDA 18-343 (captopril tablets) in response to verbal requests, and soon thereafter revised draft of medical portion of summary basis of approval for Capozide®, NDA 18-709, was provided incorporating information included in 12/28/83 and 2/9/84 submissions.
September 17, 1984	A revised package insert was submitted in response to an FDA request of August 28, 1984, for changes.

11) It is the opinion of Squibb that United States patent 4,217,347 is eligible for a 14 month extension of its term.

This 14 month period is arrived at by taking the regulatory review period for Capozide®, (which period occurred after the date the patent issued and is four years and two months) and reducing that time period by one-half of the regulatory period described in 35 U.S.C. 156(g)(1)(B)(i). This leaves a possible extension period of over two years. This is

reduced to 14 months, however, by the limitations of 35 U.S.C. 156(c)(3).

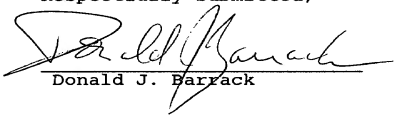
12) Squibb, and the undersigned, acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determinations to be made relative to this application for extension.

In this regard, please be aware that the components of the Capozide® products (i.e., captopril and hydrochlorothiazide) have each been previously marketed commercially after regulatory approval under section 505 of the Federal Food, Drug, and Cosmetic Act.

13) Attached hereto is a Declaration signed on behalf of Squibb which meets the criteria set forth by the United States Patent and Trademark Office at 1047 O.G. 16.

It is respectfully requested that the fee of $750.00 for this application for extension of term be charged to Deposit Account 19-3880 of E. R. Squibb & Sons, Inc. In the event the actual fee differs from that specified above, it is requested that the overpayment or underpayment be credited or charged accordingly.

Respectfully submitted,



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Pediatric Use
Safety and effectiveness in children have not been established although there is limited experience with the use of captopril in children from 2 months to 15 years of age with secondary hypertension and varying degrees of renal insufficiency. Dosage, on a weight basis, was comparable to that used in adults. CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS
Captopril
Reported incidences are based on clinical trials involving approximately 4000 patients.

Renal—One to two of 100 patients developed proteinuria (see WARNINGS).

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency.

Hematologic—Neutropenia/agranulocytosis that was probably drug related occurred in about 0.3 percent of patients treated with captopril (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash, often with pruritus, and sometimes with fever and eosinophilia, occurred in about 10 of 100 patients, usually during the first four weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10 percent of patients with skin rash have shown an eosinophilia and/or positive ANA titres. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Angioedema of the face, mucous membranes of the mouth, or of the extremities has been observed in approximately 1 of 100 patients and is reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension occurred in approximately 2 of 100 patients. See PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 2 to 3 of 1000 patients.

Dysgeusia—Approximately 7 of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited even with continued drug administration (2 to 3 months). Weight loss may be associated with the loss of taste.

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, paresthesias.

Hydrochlorothiazide
Gastrointestinal System—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, and sialadenitis.

Central Nervous System—dizziness, vertigo, paresthesias, headache, and xanthopsia.

Hematologic—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia.

Cardiovascular—orthostatic hypotension.

Hypersensitivity—purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis; cutaneous vasculitis), fever, respiratory distress including pneumonitis, and anaphylactic reactions.

Other—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, and transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Altered Laboratory Findings
Elevations of liver enzymes have been noted in a few patients but no causal relationship to captopril use has been established. Rare cases of cholestatic jaundice and of hepatocellular injury with secondary cholestasis have been reported in association with captopril administration.

A transient elevation of BUN and serum creatinine may occur, especially in patients who are volume-depleted or who have renovascular hypertension. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN.

Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE
Captopril
Correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.

Captopril may be removed from the general circulation by hemodialysis.

Hydrochlorothiazide
In addition to the expected diuresis, overdosage of thiazides may produce varying degrees of lethargy which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function.

In addition to gastric lavage and supportive therapy for stupor or coma, symptomatic treatment of gastrointestinal effects may be needed. The degree to which hydrochlorothiazide is removed by hemodialysis has not been clearly established. Measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function should be instituted.

DOSAGE AND ADMINISTRATION
DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS AND USAGE).

CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) should be taken one hour before meals.

The usual initial dose of captopril is 25 mg bid or tid. Hydrochlorothiazide is usually given at a total daily dose of 25 to 100 mg.

The approximate daily dose of captopril and hydrochlorothiazide, as determined by titration of the individual components (see INDICATIONS AND USAGE), may be administered by utilizing an appropriate potency of CAPOZIDE bid.

For example, CAPOZIDE may be administered beginning with the 25 mg/15 mg combination tablet bid. Increased captopril dosage may be obtained by utilizing the 50 mg/15 mg combination tablet bid or increased hydrochlorothiazide dosage may be obtained by utilizing the 25 mg/25 mg combination tablet bid. CAPOZIDE 25 mg/15 mg and 50 mg/15 mg tablets may also be utilized in tid dosage regimens to provide higher daily dosages.

If additional control beyond that provided by the 50 mg/15 mg tid CAPOZIDE dose is indicated, it is recommended that other antihypertensive agents be added to the regimen.

A maximum daily dose of 450 mg captopril should not be exceeded.

Beta-blockers may be used in conjunction with CAPOZIDE therapy (see PRECAUTIONS [Drug Interactions]), but the effects are less than additive. Other agents may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

For patients with very severe, accelerated or malignant hypertension; the dosage increments may be made more frequently than every two weeks with the patient under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximal dose of captopril is reached.

Dosage Adjustment in Renal Impairment—Because captopril and hydrochlorothiazide are excreted primarily by the kidneys, excretion rates reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses of CAPOZIDE.

After the desired therapeutic effect has been achieved, the dose intervals should be increased or the total daily dose reduced until the minimal effective dose is achieved. When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic is preferred for use with captopril; therefore, for patients with severe renal dysfunction the captopril-hydrochlorothiazide combination tablet is not usually recommended.

HOW SUPPLIED
CAPOZIDE (Captopril-Hydrochlorothiazide Tablets)

25 mg captopril combined with 15 mg hydrochlorothiazide in bottles of 100 (NDC 0003-0338-50) and 100 Unimatic® unit-dose packs (NDC 0003-0338-51). Tablets are white with distinct orange mottling; they are biconvex rounded squares with quadrisect bars. Tablet identification no. **338.**

25 mg captopril combined with 25 mg hydrochlorothiazide in bottles of 100 (NDC 0003-0349-50) and 100 Unimatic unit-dose packs (NDC 0003-0349-51). Tablets are peach-colored and may show slight mottling; they are biconvex rounded squares with quadrisect bars. Tablet identification no. **349.**

50 mg captopril combined with 15 mg hydrochlorothiazide in bottles of 100 (NDC 0003-0384-50) and 100 Unimatic unit-dose packs (NDC 0003-0384-51). Tablets are white with distinct orange mottling; they are biconvex ovals with a bisect bar. Tablet identification no. **384.**

50 mg captopril combined with 25 mg hydrochlorothiazide in bottles of 100 (NDC 0003-0390-50) and 100 Unimatic unit-dose packs (NDC 0003-0390-51). Tablets are peach-colored and may show slight mottling; they are biconvex ovals with a bisect bar. Tablet identification no. **390.**

STORAGE
Keep bottles tightly closed (protect from moisture); do not store above 86° F

E. R. Squibb & Sons, Inc.
Princeton, NJ 08540

J4-005

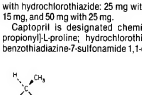
SQUIBB

CAUTION: Federal law prohibits dispensing without prescription.

CAPOZIDE® 25/15
CAPOZIDE® 25/25
CAPOZIDE® 50/15
CAPOZIDE® 50/25
Captopril-Hydrochlorothiazide Tablets

DESCRIPTION
CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) for oral administration combines two antihypertensive agents: CAPOTEN (captopril) and hydrochlorothiazide. Captopril, the first of a new class of antihypertensive agents, is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II. Hydrochlorothiazide is a benzothiadiazide (thiazide) diuretic-antihypertensive. CAPOZIDE tablets are available in four combinations of captopril with hydrochlorothiazide: 25 mg with 15 mg, 25 mg with 25 mg, 50 mg with 15 mg, and 50 mg with 25 mg.

Captopril is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline; hydrochlorothiazide is 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Graphic formulas:



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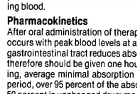
captopril



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hydrochlorothiazide

Captopril is a white to off-white crystalline powder with a slight acid-sulfhydryl odor; it is soluble in water (approx. 160 mg/ml), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate.

Hydrochlorothiazide is a white crystalline powder slightly soluble in water but freely soluble in sodium hydroxide solution.

CLINICAL PHARMACOLOGY
Captopril
Mechanism of Action
The mechanism of action of captopril has not yet been fully elucidated. It appears to act as an antihypertensive and as an adjunct in the therapy of heart failure primarily through suppression of the renin-angiotensin-aldosterone system; however, no consistent correlation has been described between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykininase," and captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. However, the effectiveness of captopril in therapeutic doses appears to be unrelated to potentiation of the actions of bradykinin.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, to small increases in serum potassium.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

Pharmacokinetics
After oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than three hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than two hours. In patients with renal impairment, however, retention of captopril occurs (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics
Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of captopril and glomerular filtration rate is usually unchanged. In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated.

Reductions of blood pressure are often maximal 60 to 90 minutes after oral administration of an individual dose of captopril. The duration of effect appears to be dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect.

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume-depleted patients. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

Studies in rats and cats indicate that captopril does not cross the blood-brain barrier to any significant extent.

Hydrochlorothiazide
Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate.

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.

The mean plasma half-life of hydrochlorothiazide in fasted individuals has been reported to be approximately 2.5 hours.

Onset of diuresis occurs in two hours and the peak effect at about four hours. Its action persists for approximately six to twelve hours. Hydrochlorothiazide is eliminated rapidly by the kidney.

INDICATIONS AND USAGE

CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) is indicated in the management of hypertension.

This fixed combination drug is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.

Because serious adverse reactions have been reported for captopril (see WARNINGS, Captopril), CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Usually, multidrug regimens include combinations of a diuretic, a sympathetic nervous system-active agent (such as a beta-blocker), and a vasodilator.

Captopril is effective alone, but in the population described above, it should usually be used in combination with a thiazide-type diuretic. The blood pressure lowering effects of captopril and thiazides appear to be additive.

CONTRAINDICATIONS

Hydrochlorothiazide

Hydrochlorothiazide is contraindicated in anuria. It is also contraindicated in patients who have previously demonstrated hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs.

WARNINGS

Captopril

Proteinuria—Total urinary proteins greater than 1 g per day were seen in 1.2 percent of patients receiving captopril and the nephrotic syndrome occurred in about one-fourth of these cases. The existence of prior renal disease increased the likelihood of the development of proteinuria. About 60 percent of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued, but some patients had persistent proteinuria. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Membranous glomerulopathy was found in nearly all of the proteinuric patients receiving captopril who were biopsied, and may be drug related. This is uncertain, however, since patients were not biopsied prior to treatment and membranous glomerulopathy may be associated with hypertension in the absence of captopril treatment.

Since most cases of proteinuria occurred by the eighth month of therapy with captopril, patients receiving captopril should have urinary protein estimates (dip-stick on first morning urine, or quantitative 24-hour urine) prior to therapy, at approximately monthly intervals for the first nine months of treatment, and periodically thereafter. When proteinuria is persistent and/or at low levels, 24-hour quantitative determinations provide greater precision. For patients who develop proteinuria exceeding 1 g/day, or proteinuria that is increasing, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (< 300/mm³) associated with myeloid hypoplasia (that was probably drug related) was observed in about 0.3 percent of patients treated with captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal functional impairment, and about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder. Multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function.

The neutropenia appeared 3 to 12 weeks after starting captopril, and it developed relatively slowly, the white count falling to its nadir over 10 to 30 days. Neutrophils returned to normal in about two weeks (other than in two patients who died of sepsis).

Captopril should be used with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response.

In patients at particular risk (as noted above), white blood cell and differential counts should be performed before starting treatment, at approximately two-week intervals for about the first three months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller, and it is sufficient in these patients to have white blood cell counts every two weeks for the first three months of captopril therapy, and periodically thereafter. Differential counts should be performed when leukocytes are < 4000/mm³, or the pretreatment white count is halved.

All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever). If infection is suspected, counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) the physician should withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in severely salt/volume depleted persons such as those treated vigorously with diuretics, for example, patients with severe congestive heart failure (see PRECAUTIONS [Drug Interactions]).

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS

General

Captopril

Impaired Renal Function—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion (see CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS (Altered Laboratory Findings)).

Surgery/Anesthesia—In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance; namely hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs, irrespective of cause include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because captopril reduces the production of aldosterone, concomitant therapy with captopril reduces the diuretic-induced hypokalemia. Fewer patients may require potassium supplements and/or foods with a high potassium content (see Drug Interactions, Agents Increasing Serum Potassium).

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Diabetes mellitus which has been latent may be manifest during thiazide administration.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, as indicated by rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism have not been seen.

Information for Patients

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.

Patients should be informed that CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) should be taken one hour before meals (see DOSAGE AND ADMINISTRATION).

Laboratory Tests

Serum and urine electrolyte levels should be regularly monitored (see WARNINGS, [Captopril and Hydrochlorothiazide], also PRECAUTIONS [General, Hydrochlorothiazide]).

Drug Interactions

Captopril

Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure within the first three hours after receiving the initial dose of captopril.

The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with captopril. Alternatively, careful medical supervision for at least three hours after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Having Vasodilator Activity: Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If resumed during captopril therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Agents Causing Renin Release: Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity: The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

Agents Increasing Serum Potassium: Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements, should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—hyperglycemia induced by thiazides may require dosage adjustment of the antidiabetic drug.

Other antihypertensive drugs—additive effect or potentiation. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Pressethetic and anesthetic agents—effects of preanesthetic and anesthetic agents may be potentiated; adjust dosage of these agents accordingly.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics; diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with CAPOZIDE.

Drug/Laboratory Test Interactions

Captopril

Captopril may cause a false-positive urine test for acetone.

Hydrochlorothiazide

Thiazides should be discontinued before carrying out tests for parathyroid function (see PRECAUTIONS [General, Hydrochlorothiazide]).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Captopril

Two year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Captopril was not mutagenic in seven standard assay systems, and studies in rats have revealed no impairment of fertility.

Animal Toxicology

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys at doses 7 to 200 times the MRHD in rats and mice, at 20 to 60 times MRHD in monkeys, and at 30 times the MRHD in dogs.

Gastric erosions/ulcerations were increased in incidence at 20 and 200 times MRHD in male rats and at 30 and 65 times MRHD in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD for only five to seven days.

In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7 to 200 times MRHD) in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

Hydrochlorothiazide

Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether this drug affects fertility in males or females.

Pregnancy—Category C

Captopril

Captopril was embryocidal in rabbits when given in doses 2 to 70 times (on a mg/kg basis) the maximum recommended human dose. The marked embryocidal effect in rabbits was most probably due to the particularly marked decrease in blood pressure caused by the drug in this species.

Captopril given to pregnant rats at 40 times the recommended human dose continuously during gestation and lactation caused a reduction in neonatal survival.

No teratogenic effects (malformations) have been observed after large doses of captopril in hamsters, rats, and rabbits.

Hydrochlorothiazide

Teratology studies have been performed in pregnant rats using captopril and hydrochlorothiazide individually and in combination; each agent was administered in doses up to 1350 mg/kg (400 times the maximum recommended human dose for hydrochlorothiazide). No evidence of embryotoxicity, fetotoxicity, or teratogenicity was found in any group.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CAPOZIDE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy—Nonteratogenic Effects

Hydrochlorothiazide

Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers

Both captopril and hydrochlorothiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) to the mother.

HA160a (1)

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 4,217,347 Dated August 12, 1980

Inventor(s) Zola P. Horovitz, et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 2, line 38, delete the hyphen between methyl and propanoyl

Column 7, line 21, insert a * above the "A"

Column 7, line 68, "means" should read --mean--

Signed and Sealed this

Third Day of February 1981

Attest:

Ruth M. Wrong

Attesting Officer

Rene D. Tegtmeyer

RENE D. TEGTMEYER

Acting Commissioner of Patents and Trademarks

United States Patent [19]

Horovitz et al.

[54] **METHOD OF TREATING HYPERTENSION AND MEDICAMENTS THEREFOR**

[75] Inventors: **Zola P. Horovitz**, Princeton; **Bernard Rubin**, Lawrence Township, Cumberland County, both of N.J.

[73] Assignee: **E. R. Squibb & Sons, Inc.**, Princeton, N.J.

[21] Appl. No.: **958,062**

[22] Filed: **Nov. 9, 1978**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 864,428, Dec. 27, 1977, abandoned.

[51] **Int. Cl.**[2] **A61K 31/54**; A61K 31/415
[52] **U.S. Cl.** **424/246**; 424/274
[58] **Field of Search** 424/274, 246

[56] **References Cited**

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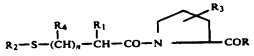
Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Lawrence S. Levinson; Donald J. Barrack

METHOD OF TREATING HYPERTENSION AND MEDICAMENTS THEREFOR

This application is a continuation-in-part of application Ser. No. 864,428, filed Dec. 27, 1977 and now abandoned.

SUMMARY OF THE INVENTION

The present invention relates to a method for reducing or alleviating hypertension with a combination comprising an effective amount of a compound of the fomula



(I)

wherein:

R is hydroxy, lower alkoxy or NH_2;

R_1 and R_4 each is hydrogen, lower alkyl or phenyl-lower alkyl;

R_2 is hydrogen or R_5-CO;

R_3 is hydrogen, hydroxy or lower alkyl;

R_5 is lower alkyl, phenyl or phenyl-lower alkyl; and

n is 0, 1 or 2.

with an effective amount of a diuretic compound and such a combination of medicaments.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of formula I have been reported to be angiotensin converting enzyme inhibitors which intervene in the angiotensinogen→renin→angiotensin I→angiotensin II mechanisn and are effective in reducing or alleviating hypertension. See U.S. Pat. No. 4,046,889, Sept. 6, 1977; Science 196, 441-443 (1977). It has been found that such compounds can be used in an oral dosage range of about 0.1 to 100 mg/kg per day and are most effective when provided at a total daily dosage of about 60 to 600 mg. Dosages within this range achieve a substantial reduction in arterial blood pressure and, in most instances, little, if any significant reduction is obtained by further increasing the dosage. Although certain peptides, teprotide (SQ20,881) for example, have been reported to have angiotensin converting enzyme activity, they are not of practical use for such an indication because of the cost and particularly since they are ineffective when orally administered [Rubin et al., 204, Jour. Pharm. Exper. Ther. 271-280, 1978; Laffan et al., Jour. Pharm. Exper. Ther. 204, 281-288, 1978; Brit. Med. Jour. 2(6141):866, 1978].

Hypertension is also frequently treated by the administration of a diuretic. Typically, treatment with an antihypertensive agent alone results in a compensatory retention of sodium and water which concomitant administration of a diuretic prevents (Wollam et al., Drugs 14:420-460, 1977). However, administration of a compound of formula I does not result in sodium and water retention when administered alone and, in fact, may by itself cause natriuresis and diuresis (Bengis et al, Circulation Research, Vol. 43 I-45-I-53, 1978). Therefore, a diuretic would not be expected to enhance the antihypertensive action of compounds of formula I. However, it has been demonstrated that the administration of a diuretic in combination with compounds of formula I is more effective than either drug alone. The combination of such compounds with a diuretic as described below

results in a potentiation of the reduction in blood pressure significantly beyond that level which either substance can achieve itself at a dosage within the acceptable range and also at lower dosage levels.

This invention therefore relates to a combination of a compound having formula I above and a diuretic of the group consisting of the thiazide class, e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methychlothiazide, trichlormethiazide, polythiazide or benzthiazide, as well as ethacrynic acid, ticrynafen, chlorthalidone, furosemide, bumetanide, triamterene, amiloride and spironolactone, and salts of such compounds, compositions comprising a combination of such compounds and to a method for alleviating hypertension with a combination of compounds.

Preferred are those compounds of formula I wherein R is hydroxy or lower alkoxy, especially C_1–C_4 lower alkoxy; R_1 is hydrogen or lower alkyl, especially methyl, R_2 is hydrogen or lower alkanoyl, especially C_2–C_4 lower alkanoyl; R_3 is hydrogen or hydroxy, especially 4-hydroxy; R_4 is hydrogen or lower alkyl, especially C_1–C_4 lower alkyl; and n is 0 or 1. Especially preferred in this group are compounds of formula I wherein R is hydroxy; R_1 is hydrogen or methyl; R_2 is hydrogen or acetyl; R_3 is hydrogen; R_4 is hydrogen or methyl; and n is 0 or 1. The especially preferred embodiment includes a compound of formula I wherein R is hydroxy; R_1 is methyl; R_2, R_3 and R_4 each is hydrogen; and n is 1, most especially (D-3-mercapto-2-methylpropanoyl)-L-proline.

Preferred as the second component of the combination is chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triamterene, especially hydrochlorothiazide or furosemide.

The especially preferred embodiments are compositions comprising (D-3-mercapto-2-methyl-propanoyl)-L-proline with either hydrochlorothiazide or furosemide.

The compounds of formula I can be produced as described in U.S. Pat. No. 4,046,889, Sept. 6, 1977. The diuretic members of the combination are known compounds which are produced by methods described in the literature.

According to this invention, a combination of a compound of formula I and a diuretic is administered in an effective amount which comprises a total daily dosage of about 30 to 600 mg., preferably 30 to 300 mg. of a compound of formula I and about 15 to 300 mg. preferably 15 to 200 mg. of the diuretic to a mammalian species which has elevated blood pressure. Such total daily dosages can be used in a single administration of the total amount or in divided doses two to four times daily. Generally, a t.i.d. or q.i.d. regimen is preferred. This preferred dosage is about 10 to 100 mg. of the compound of formula I and about 5 to 75 mg. of the diuretic three times daily or about 5 to 125 mg. of the compound of formula I and about 2.5 to 50 mg. of the diuretic four times daily. The preferred route of administration is oral.

According to one preferred embodiment, the substances can be formulated in a single pharmaceutical dosage form for oral administration such as tablet, capsule, solution or suspension comprising an effective amount of each of the active ingredients in a physiologically acceptable carrier therefor.

The active substances in the dosage unit are present in a ratio of about 1:2 to about 12:1, preferably about 2.5:1 to about 10:1, of the compound of formula I with respect to the diuretic (by weight). Generally, about 10 to 200 mg. of a compound of formula I and about 2.5 to 100 mg. of the second component can be readily formulated in the composition.

Tablets of various sizes can be prepared, e.g., of about 50 to 700 mg. in total weight, containing the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier or other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of the compound of formula I and the diuretic are more convenient and are preferred, expecially in tablet or capsule form for oral administration.

In formulating the compositions of this invention the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Many of the active substances described above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The following examples are illustrative of the invention and constitute especially preferred embodiments. They also serve as models for the preparation of other members of the group which can be produced by suitable substitution of ingredients as described above.

EXAMPLE 1

6000 tablets each containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	100	mg.
Avicel (microcrystalline cellulose)	100	mg.
Hydrochlorothiazide	12.5	mg.
Lactose U.S.P.	113	mg.
Corn starch U.S.P.	17.5	mg.
Stearic acid U.S.P.	7	mg.
	350	mg.

are produced (from sufficient bulk quantities) by slugging the (D-3-mercapto-2-methylpropanoyl)-L-proline, Avicel and a portion of the stearic acid. The slugs are ground and passed through a #2 screen, then mixed with the hydrochlorothiazide, lactose, corn starch and remainder of the stearic acid. The mixture is compressed into 350 mg. capsule shaped tablets in a tablet press. The tablets are scored for dividing in half.

EXAMPLE 2

10,000 tablets each containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	200	mg.
Corn starch U.S.P.	17.5	mg.
Lactose U.S.P.	215.4	mg.
Acacia U.S.P.	10.6	mg.
Water qs	(ca. 0.03 ml.)	
Hydrochlorothiazide	25	mg.
Corn starch U.S.P.	17.5	mg.
Avicel	200	mg.
Stearic Acid	14	mg.
	700	mg.

are produced from sufficient bulk quantities as follows: The acacia is dissolved in water. 17.5 mg. of corn starch, the (D-3-mercapto-2-methylpropanoyl)-L-proline and lactose are mixed thoroughly. The dry mixture is granulated using the aqueous solution of acacia. The granulation is wet screened, dried at 120° F. and reduced. The reduced, dry granulation is mixed with the hydrochlorothiazide and the remaining excipients are then added and mixed. The mixture is compressed into tablets of 700 mg. each.

EXAMPLE 3

Tablets each containing the following ingredients are made as described in Example 2:

(D-3-mercapto-2-methylpropanoyl)-L-proline	75	mg.
Corn starch U.S.P.	8	mg.
Lactose U.S.P.	120	mg.
Acacia U.S.P.	6	mg.
Water qs.	(ca. 0.03 ml.)	
Chlorothiazide	50	mg.
Corn starch U.S.P.	8	mg.
Avicel	75	mg.
Stearic acid	8	mg.

-continued

	350	mg.

EXAMPLE 4

1000 capsules, each containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	100	mg.
Lactose U.S.P.	211.8	mg.
Magnesium stearate	3.2	mg.
Hydrochlorothiazide	10	mg.
	325	mg.

are produced by dry blending the bulk materials (except the magnesium stearate) in a Hobart mixer, then passing the blend through a #20 screen. The materials are mixed again in the Hobart mixer with the magnesium stearate. The mixture is then filled into #2 two-piece gelatin capsules.

EXAMPLE 5

By substituting 10 mg. of furosemide for the hydrochlorothiazide in Example 4, capsules containing furosemide and (D-3-mercapto-2-methylpropanoyl)-L-proline are similarly produced.

EXAMPLE 6

By following the proceudre of Example 2 but substituting 20 mg. of furosemide for the hydrochlorothiazide and using 220.4 mg. of lactose, 700 mg. tablets each containing 20 mg. of furosemide and 200 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline are similarly produced.

EXAMPLE 7

By substituting 10 mg. of furosemide for the hydrochlorothiazide and using 115.5 mg. of lactose in the procedure of Example 1, 350 mg. scored tablets each containing 10 mg. of furosemide and 100 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline are similarly produced.

EXAMPLE 8

6000 scored tablets of 400 mg. each and containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	125	mg.
Corn starch	8	mg.
Lactose U.S.P.	95	mg.
Acacia	7	mg.
Water qs.	(ca. 0.03 ml.)	
Triamterene	50	mg.
Corn starch U.S.P.	8	mg.
Avicel	100	mg.
Stearic acid	7	mg.
	400	mg.

are produced as described in Example 2.

EXAMPLE 9

6000 scored tablets of 350 mg. each and containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	100	mg.
Avicel	100	mg.
Triamterene	25	mg.
Lactose U.S.P.	100	mg.
Corn starch U.S.P.	17	mg.
Stearic acid	8	mg.
	350	mg.

are produced as described in Example 1.

EXAMPLE 10

5000 scored tablets of 180 mg. each and containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	10	mg.
Avicel	50	mg.
Hydrochlorothiazide	5	mg.
Lactose U.S.P.	101	mg.
Corn starch U.S.P.	10	mg.
Stearic acid	4	mg.
	180	mg.

are produced as described in Example 1.

EXAMPLE 11

By substituting the same amount of ticrynafen for the hydrochlorothiazide in Example 1, tablets containing 100 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline and 12.5 mg. of ticrynafen are similarly obtained.

Representative of the results obtained with combinations of agents of this invention are data obtained from studies in spontaneously hypertensive rats and two kidney renal hypertensive rats.

(A) In an acute study with spontaneously hypertensive rats, ten to fourteen week old male Wistar-Kyoto spontaneously hypertensive rats (190–210 gm.) of the Okamoto-Aoki strain (obtained from Taconic Farms, Germantown, N.Y.) were given food and water ad libitum and intubated according to the method of Weeks and Jones, Proc. Soc. Exp. Biol. Med. 104, 646–648 (1960), to prepare them for blood pressure and heart rate determination by implanting indwelling abdominal aortic catheters under sodium pentobarbital anesthesia.

Three weeks later their direct blood pressure and heart rate were recorded by the method of Laffan et al., Cardiovasc. Res. 6, 319–324 (1972), modified as follows. The signal from the transducer was digitized in a 10 bit A/D converter and input to a PDP 11/05 computer. The computer was programmed to sense and store samples at a rate of 125/sec for each rat, as well as the number of pressure pulses during 10 sec. of each scan on each rat. These parameters were averaged and stored as the MBP (mean blood pressure, mm Hg) and heart rate (beats/min.) for that time. Data were acquired from each rat every five minutes. Six such sets of data were averaged to give a mean value representing a 30 minute sample and this 30 minute figure was stored for subsequent analysis. Each time a 48 hour cycle was completed (or sooner if demanded) the data were transferred serially to a host computer (PDP 11/40) for further analysis and the data were printed out on a Versatec Printer/Plotter for at least 16 hours after each dose.

The spontaneously hypertensive rats were segregated into four groups of five rats each (except group 3 which included six rats). The following was administered to the rats in the respective groups:

1. (Control) Agar-5 ml./kg + agar-5 ml./kg
2. Water-5 ml./kg + Compound A-30 mg./kg
3. Compound F** -50 mg./kg + Agar-5 ml./kg
4. Compound F** -50 mg./kg + Compound A* -30 mg./kg

* Compound A = (D-3-mercapto-2-methylpropanoyl)-L-proline
** Compound F = Furosemide

Compound F was suspended in 0.25% agar and Compound A was in aqueous solution. All substances were administered by gavage and there was a one hour interval between drugs. Test results were evaluated 2.5 hours after single oral doses.

The following results were obtained:

TABLE I

	Mean Blood Pressure (mm/Hg)	
	Before	2.5 hours after single oral dose
(1)	173	169
(2)	175	158
(3)	184	172
(4)	177	128

In these studies Compound F alone, 50 mg./kg. p.o., produced a 9.7% decrease in SHR blood pressure. Compound A alone, 30 mg./kg., produced 6.5% decrease in blood pressure. The combination of Compound A, 30 mg./kg., p.o., + Compound B, 50 mg./kg., p.o., reduced blood pressure in SHR rats by 27.7%.

(B) In chronic studies with renal hypertensive rats, male rats (115–150 g.) of the Charles River Sprague Dawley (COBS-CO) strain were anesthetized with ether and a silver clip (0.22 mm i.d.) was placed on the left renal artery through a flank incision. The contralateral kidney was left intact (two-kidney Goldblatt model: 2-K RHR). Each rat was fitted with a tail cuff for air inflation and a Korotkoff sound microphone for the detection of arterial pulsation. An oscilloscope was used for a visual appearance and disappearance of the pulse. Blood pressure measurements were determined after a minimum of six inflations with systolic pressures observed on a Narco physiograph manometer. Blood pressures were determined initially just prior to dosing and twice weekly at 4 hours after dosing.

The number of rats in each group was 15. Single daily treatments were made by gavage with crossover treatments as indicated in the table below. The control group received distilled water. Compound A was administered in distilled water, 30 mg./kg. Compound H was administered in 0.25% methylcellulose. The means

blood pressure (mm/Hg.) for each group before dosing and on day 119 (4 hours after dosing) and the number of survivors on day 120 is shown in the table.

TABLE II

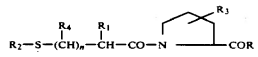
Group	Treatment	Crossover Treatment*	Mean Blood Pressure Initial	Mean Blood Pressure Day 119	No. of Survivors (%)
1	H_2O	H_2O	198 ± 4.9	207 ± 6.6	10 (66.7)
2	H_2O	H_2O + A	198 ± 4.9	206 ± 5.2	10 (66.7)
3	H_2O	H_2O + H	206 ± 7.5	207 ± 4.8	11 (73.3)
4	A	A	197 ± 5.3	167 ± 4.6	14 (93.3)
5	A	H_2O	197 ± 6.2	176 ± 5.1	14 (93.3)
6	A	A# + H#	202 ± 6.6	140 ± 4.6	15 (100)
7	H	H	197 ± 5.8	202 ± 8.4	8 (53.3)

*Crossover took place on day 28 through day 33 and on day 91 through day 96 (except Group 6 - see below).
#Daily dosage of each maintained from day 109 on.
A = (D-3-mercapto-2-methylpropanoyl)-L-proline
H = Hydrochlorothiazide

The foregoing data show that on long term treatment compound H shows no significant decrease in blood pressure. Compound A alone shows approximately a 10 to 15% reduction in blood pressure. The combination dosing with Compound A and Compound H shows approximately a 30% reduction in blood pressure. Moreover, the combination is the only one showing a 100% survivor rate.

What is claimed is:

1. A method for reducing blood pressure which comprises orally administering to a mammalian species having elevated blood pressure a daily dosage of a combination comprising about 30 to 600 mg. of a compound having the formula



wherein:

R is hydroxy, lower alkoxy or NH_2;

R_1 and R_4 each is hydrogen, lower alkyl or phenyl-lower alkyl;

R_2 is hydrogen or R_5-CO;

R_3 is hydrogen, hydroxy or lower alkyl;

R_5 is lower alkyl, phenyl or phenyl-lower alkyl; and

n is 0, 1 or 2

and about 15 to 300 mg. of a diuretic selected from the group consisting of chlorothiazide, hydrochlorothiazide, flumethiazide, amiloride, hydroflumethiazide, bendroflumethiazide, methyclothiazide, trichlormethiazide, polythiazide, benzthiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosemide, bumetanide, triamterene and spironolactone or salts of said compounds.

2. A method as in claim 1 wherein the combination comprises about 30 to 300 mg. of the compound of the formula and about 15 to 200 mg. of the diuretic.

3. A method as in claim 1 wherein the compound of the formula has R as hydroxy or lower alkoxy; R_1 as hydrogen or lower alkyl; R_2 as hydrogen or lower alkanoyl; R_3 as hydrogen or hydroxy; R_4 as hydrogen or lower alkyl; and n as 0 or 1.

4. A method as in claim 1 wherein the compound of the formula has R as hydroxy; R_1 as hydrogen or methyl; R_2 as hydrogen or acetyl; R_3 as hydrogen; R_4 as hydrogen or methyl; and n as 0 or 1.

5. A method as in claim 1 wherein the diuretic is chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triameterene.

6. A method as in claim 1 wherein the diuretic is hydrochlorothiazide or furosemide.

7. A method as in claim 1 wherein the compound of the formula has R as hydrogen or lower alkoxy; R_1 as hydrogen or lower alkyl; R_2 as hydrogen or lower alkanoyl; R_3 as hydrogen or hydroxy; R_4 as hydrogen or lower alkyl; and n as 0 or 1; and the diuretic is chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triamterene.

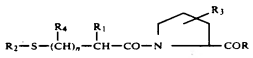
8. A method as in claim 1 comprising about 30 to 300 mg. of a compound of the formula wherein R is hydroxy or lower alkoxy; R_1 and R_4 each is hydrogen or lower alkyl; R_2 is hydrogen or lower alkanoyl, R_3 is hydrogen or hydroxy; and n is 0 or 1, and about 15 to 200 mg. of chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triamterene.

9. A method as in claim 1 wherein the compound of the formula is (D-3-mercapto-2-methylpropanoyl)-L-proline and the diuretic is hydrochlorothiazide or furosemide.

10. A method as in claim 1 wherein the compound of the formula is (D-3-mercapto-2-methylpropanoyl)-L-proline in an amount of about 30 to 300 mg. and the diuretic is hydrochlorothiazide in an amount of about 15 to 200 mg.

11. A method as in claim 1 wherein the compound of the formula is (D-3-mercapto-2-methylpropanoyl)-L-proline in an amount of about 30 to 300 mg. and the diuretic is furosemide in an amount of about 15 to 200 mg.

12. An oral antihypertensive composition comprising about 30 to 600 mg. of a compound of the formula



wherein:

R is hydroxy, lower alkoxy or NH_2;

R_1 and R_4 each is hydrogen, lower alkyl or phenyl-lower alkyl;

R_2 is hydrogen or R_5-CO;

R_3 is hydrogen, hydroxy or lower alkyl;

R_5 is lower alkyl, phenyl or phenyl-lower alkyl;

n is 0, 1 or 2,

about 15 to 300 mg. of a diuretic selected from the group consisting of chlorothiazide, hydrochlorothiazide, amiloride, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylclothiazide, trichlormethiazide, polythiazide, benzthiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosemide, bumetanide, triamterene, spironolactone and salts thereof, and a physiologically acceptable carrier therefor.

13. A composition as in claim 12 comprising about 30 to 300 mg. of the compound of the formula and about 15 to 200 mg. of the diuretic.

14. A composition as in claim 12 wherein the compound of the formula has R as hydroxy or lower alkoxy; R_1 as hydrogen or lower alkyl; R_2 as hydrogen or lower

alkanoyl; R_3 as hydrogen or hydroxy; R_4 as hydrogen or lower alkyl; and n as 0 or 1.

15. A composition as in claim **12** wherein the compound of the formula has R as hydroxy; R_1 as hydrogen or methyl; R_2 as hydrogen or acetyl; R_3 as hydrogen; R_4 as hydrogen or methyl; and n as 0 or 1.

16. A composition as in claim **12** wherein the diuretic is chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triamterene.

17. A composition as in claim **12** wherein the diuretic is hydrochlorothiazide or furosemide.

18. A composition as in claim **12** wherein the compound of the formula has R as hydrogen or lower alkoxy; R_1 as hydrogen or lower alkyl; R_2 as hydrogen or lower alkanoyl; R_3 as hydrogen or hydroxy; R_4 as hydrogen or lower alkyl; and n as 0 or 1; and the diuretic is chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triamterene.

19. A composition as in claim **12** wherein the compound of the formula is (D-3-mercapto-2-methylpropanoyl)-L-proline and the diuretic is hydrochlorothiazide or furosemide.

20. A composition as in claim **12** comprising about 30 to 300 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline and about 15 to 200 mg. of hydrochlorothiazide.

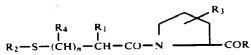
21. A composition as in claim **13** comprising about 30 to 300 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline and about 15 to 200 mg. of furosemide.

22. A composition as in claim **25** comprising about 5 to 125 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline and about 2.5 to 50 mg. of hydrochlorothiazide.

23. A composition as in claim **25** comprising about 5 to 125 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline and about 2.5 to 50 mg. of furosemide.

24. An oral hypertensive composition comprising about 5 to 125 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline and about 5 to 75 mg. of triamterene.

25. An oral antihypertensive composition comprising about 5 to 125 mg. of a compound of the formula



wherein:

R is hydroxy, lower alkoxy or NH_2;

R_1 and R_4 each is hydrogen, lower alkyl or phenyl-lower alkyl;

R_2 is hydrogen or R_5-CO;

R_3 is hydrogen, hydroxy or lower alkyl;

R_5 is lower alkyl, phenyl or phenyl-lower alkyl; and

n is 0, 1 or 2, about 2.5 to 50 mg. of a diuretic selected from the group consisting of chlorothiazide, hydrochlorothiazide, amiloride, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylclothiazide, trichlormethiazide, polythiazide, benzthiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosemide, bumetanide, triamterene, spironolactone and salts thereof, and a physiologically acceptable carrier therefor.

* * * * *

[57] **ABSTRACT**

A method for reducing blood pressure comprises administering a combination of a diuretic compound and a compound having the general formula